



on behalf of the British Menopause Society (2020). Risks and benefits of hormone replacement therapy before and after a breast cancer diagnosis. *Post-Reproductive Health*.
<https://doi.org/10.1177/2053369120934026>

Peer reviewed version

Link to published version (if available):
[10.1177/2053369120934026](https://doi.org/10.1177/2053369120934026)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via SAGE Publications at <https://journals.sagepub.com/doi/10.1177/2053369120934026> . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

BMS Consensus Statement
The Risks and Benefits of HRT before and after a Breast Cancer Diagnosis
Jo Marsden, Hugo Pedder on behalf of The British Menopause Society with acknowledgement to
Professor Richard Santen

Introduction

This is an important and controversial topic. The risk of breast cancer diagnosis associated with hormone replacement therapy (HRT) is often assumed by health care professionals and the lay public alike to be very high, which may adversely influence decisions about its initiation and continuance.¹ This is despite the fact that most women will not be diagnosed in their lifetime and any risk conferred by HRT is less than that of other postmenopausal lifestyle risk factors for breast cancer (e.g. obesity, alcohol).² The impact of HRT on breast cancer diagnosis is often discussed in isolation of its benefits and there is no or little simultaneous reference to the other lifestyle risk factors for breast cancer, to provide context when counselling women about its use. This consensus statement provides an overview of the association between HRT and breast cancer outcomes in women at low and higher risk of breast cancer. It had been updated in light of the recent publication from the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC), which has stoked further concern.³ A summary of recommendations for clinical practice is provided at the end of this statement.

HRT and the risk of being diagnosed with breast cancer, studies pre-dating the 2019 CGHFBC

To aid interpretation of the 2019 CGHFBC, key publications pre-dating it, which have influenced UK HRT prescribing practice are reviewed. Those that have largely shaped clinical practice include the 1997 CGHFBC re-analysis of 51 world-wide observational studies, the placebo-controlled, randomised Women's Health Initiative Study (WHI), observational Million Women's Study (MWS) and the 2015 National Institute for Health and Care and Excellence Menopause Guidance (NG23).⁴⁻⁸ In considering the findings from all these studies, it is relevant to keep in mind that whilst analysis of large patient cohorts such as the MWS, the CGHFBC re-analyses and 2015 NG23 will produce statistical precision, reliability is limited due to the risk of bias and confounding inherent in observational methodology. The WHI placebo-controlled data is likely to provide a better estimate of the relative risk for HRT versus placebo.

1. The 1997 CGHFBC established a duration-dependent association of HRT with risk of diagnosis, emerging after 5 years' exposure (an overall risk ratio of 1.35). This appeared greater with combined rather than unopposed HRT and fell following cessation. The degree of risk with any HRT exposure was estimated to be equivalent to the impact of a delayed menopause (2.3% vs 2.8% per year respectively).⁴
2. In 2002 and 2004, initial findings from the randomised WHI study confirmed an overall increased risk of borderline significance with continuous combined HRT (i.e. 0.625mg conjugated equine oestrogen, CEE plus 2.5mg medroxyprogesterone acetate). Risk was not significantly increased, however, when subgroup analysis was performed by age group (i.e. 50 to 59, 60 to 69 and 70 to 79 years).⁵ Unopposed oestrogen (i.e. 0.625mg CEE) was associated with a non-significant reduction in risk of diagnosis.⁶ These contrasting outcomes can be explained by the effect of HRT on the reservoir of occult hormone sensitive cancers present in the breast at the time of its initiation. When deprived of oestrogen long-term, breast epithelium becomes susceptible to oestrogen-induced apoptosis upon oestrogen re-exposure. Hence, in hormone naïve postmenopausal women, commencement of unopposed oestrogen reduces the growth of any occult breast cancers so they take longer to reach the size threshold for diagnosis and a decrease in risk of diagnosis is observed. Exposure to combined HRT is hypothesised to stimulate occult breast cancer growth leading to them reaching their size threshold for diagnosis sooner, therefore risk of diagnosis is increased.⁹

3. In 2003, the observational MWS reported risk of diagnosis to be increased with *all* HRT regimens, the greatest elevation in risk associated with combined preparations. In contrast with all other studies, the impact of HRT was observed with short-term use risk (i.e. 6 months to less than 2 years).⁷ This erroneous finding has been attributed to ascertainment bias and underestimation of duration of HRT exposure. Further criticisms of the study methodology have been explained in detail elsewhere.¹⁰

Unfortunately, whilst the degree of estimated risk with combined HRT from the randomised WHI was between 1.2-1.3 and that of the MWS was in keeping with the 1997 CGHFBC and other observational study risk estimates (i.e. up to twofold increase), the adverse publicity their results generated caused a significant fall in HRT prescribing world-wide. Both study investigators placed emphasis on use of risk ratios and percentage change in risk, which were misinterpreted and could have been avoided by presenting findings using absolute numbers with framing.¹¹

4. The 2015 NG23 included evaluation of the short-term outcomes of HRT, with use for up to 5 years on breast cancer outcomes.⁸ The clinical studies eligible for review were mostly observational and ranged from low to moderate quality at best. Of randomised trials, only the WHI study was sufficiently powered for inclusion. Overall the findings did not differ significantly from those of previous evidence.

Taken as a whole, clinical evidence *predating* the 2019 CGHFBC led to the following conclusions:

- HRT with oestrogen alone (CEE, oestradiol, oestriol) is associated with no or little change in risk and may not be increased with low-dose vaginal oestrogen.^{8,12}
- Combined HRT, delivered by any route of administration, can be associated with an increased risk, which appears duration dependent.^{8,13,14} Evidence for the levonorgestrel intra-uterine system (LNG-IUS) is inconsistent.^{15,16} Risk may not be elevated if dydrogesterone or micronized progesterone are used in preference to synthetic progestogens but further confirmatory evidence is needed.^{12,13,17}
- Risk of diagnosis is not elevated in past users of HRT⁸
- Risk is limited to lean women (i.e. not overweight or obese)⁴
- There does not appear to be a dosage effect¹⁴
- There is no additive effect in women at elevated personal risk due to a family history or high-risk benign breast condition.^{4,14}
- In women with premature ovarian insufficiency (POI), it is recommended that years of HRT exposure should be counted from the age of 50 and not at the age of HRT commencement when POI is diagnosed.^{4,18}

The 2019 CGHFBC

Despite this re-analysis involving data from 58 published *and* unpublished, worldwide observational studies, the main outcomes reported were restricted to data from 24 prospective studies, which contributed 75% of the cases, half of these were from the widely criticised MWS. No results from the placebo controlled, WHI study were shown for comparison in the main paper.

The main findings are as follows:

1. The risk of breast cancer diagnosis is greater with combined than unopposed HRT
 - i. In common with previous evidence, a duration-dependent increase in risk was associated with sequential *and* continuous combined preparations, risk with the latter being greater.¹⁷
 - ii. The difference in *absolute* risk, however, between continuous and sequential combined HRT is small, with up to 14 years exposure an estimated excess difference of 10 additional breast cancer diagnoses per 1000 women aged between 50 to 59 respectively. This should be weighed against the risk of endometrial cancer which is significantly decreased by continuous but not sequential prescription of HRT.¹⁹

- iii. As in previous studies short-term use for up to 5 years of dydrogesterone and micronized progesterone-containing regimens were not associated with an increased risk of diagnosis but a longer duration of exposure was.^{4,17} However, whilst increased risk with a longer duration of dydrogesterone use was less than that of synthetic progestogens, no meaningful conclusions can be drawn for micronized progesterone as the number of breast cancer events was too small for reliable estimation.⁴
- iv. Unopposed oestrogen was reported to be associated with an increased risk of breast cancer diagnosis, which differs with the randomised WHI study, where a decreased risk of diagnosis was reported with unopposed CEE.⁶ These apparent opposing effects of unopposed oestrogen on risk of diagnosis can be explained by the oestrogen deprivation hypothesis in which, the duration of a woman's endogenous oestrogen depletion determines whether apoptosis of pre-existing, occult breast cancers occurs upon oestrogen re-exposure with unopposed HRT. Short-term oestradiol depletion is not associated with apoptosis upon re-exposure, whereas long-term oestradiol deprivation is.⁹
 - a. The breast tissue in women recently postmenopausal is only short-term oestradiol deprived. Hence initiation of unopposed HRT does not cause apoptosis but stimulates proliferation of pre-existing, occult breast cancers. As this proliferative effect is much less than that of estrogen plus a progestogen, it takes a much longer time to detect an increased risk of breast cancer diagnosis with oestrogen alone. This would explain the CGHFBC finding that women commencing oestrogen alone shortly after the menopause appear to have no increase in breast cancer if used over a period of 5 years but with more prolonged use risk of diagnosis increases.
 - b. In contrast, older postmenopausal women will have been depleted of oestradiol for longer and exposure to unopposed HRT stimulates apoptosis, slowing the growth of pre-existing occult breast cancers. As the average age of women in the WHI study was 63, this likely accounts for the finding of a protective effect. This appears to be supported by the CGHFBC, as in women over 60 at time of commencing unopposed HRT, the risk of breast cancer diagnosis was either not increased or reduced depending on whether analysis of prospective or retrospective observational studies was undertaken (relative risk 1.03, 95% CI 0.88-1.21 vs 0.56, 95% CI 0.46-0.68).
- v. Risk with unopposed oestrogen was elevated with oral *and* transdermal oestrogen administration but unaffected by low and ultra-low dose vaginal preparations that have minimal systemic absorption. This concurs with previous evidence.^{12,17,20}
- vi. There was no evidence of a dosage effect with unopposed oestrogen

Table 1 compares the absolute excess risk with current HRT use from the randomised WHI, 2019 CGHFBC and 2015 NG23. Overall, the absolute excess risk of diagnosis with HRT use is small, regardless of category of current use. Most women exposed to HRT will not be diagnosed with breast cancer as a result of exposure.

Absolute excess risk of breast cancer diagnosis over 10 years per 1000 women starting HRT at age 50					
	Duration of HRT use	HR or RR (95% CI)	Absolute Excess Risk	Women diagnosed	Women not diagnosed
No HRT				26	974
Oestrogen alone		-	-		
<i>Use up to 5 years^a</i>					
WHI study 2013	4.6 yrs (median)	0.62 (0.32-1.18)	-11	15	985
NICE 2015	Up to 5 years	1.16 (0.95-1.42)	+3	29	971
CGHFBC 2019 ^b	< 5 years	1.16 (1.10-1.24)	+3	29	971
<i>Use up to 10 years</i>					
WHI study 2013	No data	-	-	-	-
NICE 2015 ^b	5-10 years	1.23 (0.94-1.61)	+6	32	968
CGHFBC 2019 ^b	5-9 years	1.22 (1.17-1.28)	+6	32	968
Combined HRT					
<i>Use up to 5 years^a</i>					
WHI study 2013	3.2 yrs (median)	1.06 (0.67-1.67)	+4	30	970
NICE 2015	Up to 5 years	1.52 (1.25-1.85)	+8	34	966
CGHFBC 2019	< 5 years	1.56 (1.49-1.64)	+9	35	965
<i>Use up to 10 years</i>					
WHI study 2013	No data	-	-	-	-
NICE 2015 ^c	5-10 years	1.94 (1.41-2.66)	+24	50	950
CGHFBC 2019	5-9 years	1.97 (1.90-2.04)	+25	51	949

^a Absolute risks calculated over 10 years as 5 years HRT use, followed by 5 years past HRT use.

^b The risk estimate for less than five years category has been calculated by pooling the numbers for <1 year and one to four years duration of HRT exposure, using inverse variance weighting.

^c Evidence on observational estimate demonstrated very serious imprecision in the estimate of effect.

2. In past users of HRT, the relative risks were lower than in current users but risks remained elevated more than 10 years after stopping.
 - i. Most evidence prior to the 2019 CGHFBC showed a fall in risk of breast cancer diagnosis after HRT cessation, hence the 2015 NG23 recommendation to advise women of such.⁸ The 2019 CGHFBC finding that risk persists after stopping HRT is new and associated with a longer duration of prior use and a longer time since cessation.³
 - ii. Long-term follow-up of the randomised WHI study also showed similar trends, with an initial fall in risk after HRT cessation, followed by an elevated risk more than five years since stopping.²¹
 - iii. Both sets of results can be explained by the *growth promoting* effect of HRT on pre-existing, hormone sensitive, occult breast cancers. Withdrawal of unopposed oestrogen stops oestrogen-induced apoptosis, leading to an increase in cancer growth rate and a late-onset elevated risk of diagnosis, when the size threshold for diagnosis is eventually reached. Stopping combined HRT slows the rate of occult cancer growth resulting in an initial fall in diagnosis, followed by a late-onset increase, when the diagnostic size threshold is reached.⁹
 - iv. For both unopposed and combined HRT, the absolute excess risk in past users is small and less than that associated with being overweight or drinking 2 or more units of alcohol per day).^{3, 22}

Table 2 shows comparative absolute risks in women with a previous duration of HRT use up to five years from the 2019 CGHFBC and randomised WHI study.

Absolute excess risk of breast cancer diagnosis over 10 years per 1000 women starting HRT at age 50 with previous HRT exposure, by duration of use and time since stopping					
Prior duration of HRT use, 5 years	Time since last use	HR or RR (95% CI)	Absolute Excess Risk	Women diagnosed	Women not diagnosed
Past use of oestrogen					
No HRT		-	-	26	974
Time since stopping up to 5 years^a					
WHI study 2013, 2015	2.75 years ^c	0.55 (0.34-0.89)	-4	22	978
CGHFBC 2019	< 5 years ^d	1.05 (0.96-1.16)	+1	27	973
Time since stopping 5 to 9 years^b					
WHI study 2013, 2015	6.6 years ^e	1.17 (0.73-1.87)	-	-	-
CGHFBC 2019	5-9 years	1.06 (0.97-1.16)	+1	27	973
Past use of combined HRT					
Time since stopping up to 5 years^a					
WHI study 2013, 2015	2.75 years ^c	1.23 (0.90-1.70)	+8	34	966
CGHFBC 2019	< 5 years ^d	1.13 (1.05-1.21)	+2	28	972
Time since stopping 5 to 9 years^b					
WHI study 2013, 2015	8.2 years ^e	1.37 (1.06-1.77)	-	-	-
CGHFBC 2019	5-9 years	1.21 (1.14-1.29)	+1	27	973

^a Absolute risks calculated over 10 years as 5 years of 5 years since stopping HRT, followed by 5 years of 5-9 years since stopping HRT use.

^b Absolute risks calculated over 10 years as 5 years of 5-9 years since stopping HRT, followed by 5 years of >10 years since stopping HRT use.

^c Duration of the early intervention phase post HRT cessation.

^d The risk estimate for less than five years category has been calculated by pooling the numbers for <1 year and one to four years duration of HRT exposure, using the inverse variance weighting.

^e Duration of late intervention phase in the estrogen only and combined HRT arms.

3. Women who start HRT soon after menopause have an increased risk of invasive breast cancer, compared with never users
 - i. Risk of diagnosis was found to be increased in women who commenced HRT nearer to the time of onset of menopause compared with those starting it more than five years since menopause. However, this is relatively weak evidence, not supported by the randomised WHI study, which in itself was probably underpowered for reliable assessment of this outcome.²³
 - ii. In conclusion, there insufficient evidence currently to recommend that time from menopause should influence decision-making.
4. Use of HRT in postmenopausal women younger than 50 increases risk of breast cancer diagnosis
 - i. The 2019 CGHFBC reported that commencing HRT between the ages of 40 and 50 increases risk of diagnosis, which contradicts advice to date.³
 - ii. The control group, of age-matched postmenopausal women, however, was inappropriate as an early menopause reduces breast cancer risk. The population for comparison should have consisted of age-matched *normally cycling* women.
 - iii. The current recommendation that years of HRT exposure in women with POI should be counted from the age of natural menopause (i.e. 50) should stand. Younger peri and postmenopausal women accrue significant symptom, quality of life, bone and cardiovascular benefits from HRT.¹⁸

Placing breast cancer risk with HRT in perspective

1. HRT and other lifestyle risk factors for breast cancer

The 2015 NG23 recommended HRT counselling should be individualized, accounting for non-modifiable factors that determine a woman's personal, baseline breast cancer risk, such as family history and exposure to modifiable risk factors, which include HRT.⁸ Avoidance of modifiable risk factors has been estimated to potentially prevent just under a quarter of breast cancers diagnosed in the UK female population (23%).²² In women who are overweight or obese, or those whose alcohol intake is elevated, the population attributable risk is 8%, which is greater than that associated with any HRT exposure (including risk in past users), at 5%.^{3,22} Unfortunately, it is not possible to predict on an *individual* basis, who will benefit from minimising exposure to these.

Table 3 summarises absolute population risk estimates by age group for obesity, alcohol intake and HRT.

Lifestyle risk factors	Study	RR	Absolute excess risk per 1000 women over 5 years		
			50-54 years	55-59 years	50-59 years
Postmenopausal obesity ²⁴	Highest vs lowest weight	1.74	+9	+9	+18
	Per 5kg/m ² weight gain	1.33	+5	+4	+9
Alcohol ^{25,*}	35-44g / day	1.32	+4	+4	+8
	≥ 45g / day	1.46	+6	+6	+12
Unopposed HRT Up to 5 years use	WHI study ⁶	0.79	-3	-3	-6
	2015 NG23 ⁸	1.16	+2	+2	+4
	2019 CGHFBC ³	1.16	+2	+2	+4
Combined HRT Up to 5 years use	WHI study ⁵	1.24	+3	+3	+6
	2015 NG23 ⁸	1.52	+7	+7	+14
	2019 CGHFBC ³	1.56	+7	+7	+14

* Risk with alcohol is unaffected by menopausal status. 1 unit of alcohol = 8g

2. HRT benefits and risks

For women experiencing menopausal symptoms, with a low underlying risk of breast cancer (i.e. most of the female population), the benefits of HRT in relieving symptoms, improving quality of life and conferring protection against cardiovascular disease and osteoporosis, will exceed potential harms, which include the small increased risk of breast cancer and venous thrombo-embolic disease (VTED) diagnosis.⁸ In 2017, postmenopausal female deaths in England and Wales from ischaemic heart disease and osteoporosis combined (20,388) were almost four times that attributed to breast cancer (5,483).²⁶ HRT-associated risk of VTED can be minimised by the use of transdermal oestrogen and possibly with combined preparations containing micronized progesterone or dydrogesterone.⁸

3. HRT and mortality

i. Breast cancer mortality

The 2019 CGHFBC did not evaluate this relationship with HRT, although an accompanying research letter from the MWS investigators did.²⁷ Here current and previous HRT use for a duration of more than five years was reported to be associated with an increased risk of breast cancer death. Other meta-analyses, the 2015 NG23 and long-term follow-up of the randomised WHI study do not concur with this, although the WHI was insufficiently powered to evaluate this outcome.^{8,28,29} All evidence is open to scrutiny as collectively there is failure to provide adequate information about disease stage, treatment and mode of breast cancer diagnosis (i.e. whether screen-detected or symptomatic), which have a significant impact on prognosis. Furthermore, hormone sensitive breast cancer, which is promoted by HRT, has a higher long-term relapse

pattern compared with hormone insensitive disease. Beyond five years from diagnosis, the risk of recurrence is greater and beyond fourteen years, overall survival is worse in oestrogen receptor positive cancer.³⁰

ii. All-cause mortality

In women at population risk for breast cancer, the overall mortality risk: benefit ratio favours unopposed and combined HRT.^{29,31} A recent cohort study with a follow-up of just under 18 years, however showed time-specific *differential* associations in cause of HRT-associated death with a slightly higher breast cancer mortality, however, this was offset by lower colorectal cancer and cardiovascular deaths.³¹ This illustrates how inappropriate it is to discuss HRT association with breast cancer without any consideration that a risk factor for one health condition may protect against another. The decline in unopposed oestrogen use in the USA since 2002, which has resulted in a significant increase in premature mortality for hysterectomized women aged 50 to 59 years, illustrates the relevance of fully informed patient discussion.³²

HRT in women at high baseline risk of breast cancer

In women with a familial risk or a high-risk benign breast condition (i.e. biopsy-proven epithelial atypia or Lobular Carcinoma in Situ), HRT exposure has not been shown to have an additive effect on risk of diagnosis.^{13,14} Its absolute impact therefore increases as a woman's baseline risk rises. Although it is recommended lifestyle and non-hormonal alternatives should be used as first-line management of vasomotor symptoms in high-risk women, HRT may be needed for severe, refractory symptoms and should be considered on an individual basis following specialist and patient discussion.^{8,13,14,33} In the absence of data, it would be difficult to justify use of HRT for indications other than symptom relief, where longer duration therapy would be indicated as for example in population-risk women with POI. The exception to this is BRCA1 and BRCA2 mutation carriers, who have undergone risk-reducing bilateral salpingo-oophorectomy (BSO). Here, add-back HRT has not been shown to diminish the risk-reducing benefit of BSO on subsequent risk of breast cancer diagnosis but clinical data is very limited.^{13,14} Further studies are needed to clarify risk with combined compared with unopposed HRT and the optimal duration of use.³⁴ The current recommendation is that after risk-reducing BSO, add-back HRT is used until the age of an expected natural menopause, after which non-hormonal alternatives are used as first-line management for symptom control and the prevention of chronic, oestrogen-deficiency health problems.^{13,33}

Use of HRT after breast cancer

Women treated for breast cancer may experience multiple symptoms including hot flushes and vulvo-vaginal atrophy as a consequence of a natural menopause or as a side effect of treatment aimed at reducing the activity or synthesis of oestrogen. Iatrogenic symptoms are not limited to women with hormone sensitive disease as chemotherapy-induced ovarian suppression will occur irrespective of the oestrogen receptor (ER) status of the primary tumour.³⁵ Systemic HRT and low-dose vaginal oestrogen are the most efficacious treatments but contra-indicated in women with ER positive disease. HRT, however, may not be without risk for those with an ER negative primary. Although there is high concordance in hormone receptor status between first and second primary breast cancers, a minority with an ER negative primary may present with an ER positive contralateral cancer (up to 30%) and approximately 8% may present with ER positive metastatic disease.^{36,37} It is unknown whether lifestyle risk factors have a part in this. It has been hypothesised risk will not be increased in women taking concurrent tamoxifen due to the very high binding affinity for the oestrogen receptor. However, as aromatase inhibitors reduce oestrogen production it would be counter-intuitive to prescribe concomitant exogenous sex hormones.^{8,13,14} Despite theoretical predictions, clinical evidence is inconclusive due to the premature closure of all three randomised trials of HRT in breast cancer patients, when all were underpowered. These were stopped when

interim analysis of one trial showed an increased risk of recurrence. Overall risk was not increased following interim analysis of the two other trials or meta-analysis of all three (hazard ratio 1.45, 95% confidence interval 0.93-2.26).³⁸ Tibolone, a synthetic steroid with weak oestrogen, progestogen and/or androgen activity, has been used as an alternative to HRT for symptom relief but a large randomised study in breast cancer patients was also stopped prematurely due to an increased risk of recurrence (hazard ratio HR 1.40, 95% CI 1.14-1.70).³⁹

When is it appropriate to discuss systemic or vaginal HRT in the management of women with diagnosis of a previous breast cancer?

NICE has taken a pragmatic approach, recommending lifestyle and non-hormonal alternatives for first-line management of vasomotor symptoms, recognising HRT could be considered if symptoms are refractory.^{8,35} For women with symptoms due to vulvo-vaginal atrophy if treatment with vaginal moisturisers fails to alleviate symptoms, vaginal oestrogen can be discussed.³⁴ There is generally lower concern about systemic absorption from low and ultra-low dose vaginal oestrogen, which is minimal and could be acceptable where systemic therapy would not be. Neither systemic HRT nor low-dose vaginal oestrogen are recommended in women taking an aromatase inhibitor and with both, prescription should only take place after discussion between the patient, her primary health care and breast specialist team.³⁵

Summary

The British Menopause Society is of the view that the 2019 CGHFBC re-analysis provides important additional information on the risk of breast cancer diagnosis with HRT. The only findings which should influence clinical advice is that risk does not appear to be elevated with low-dose vaginal oestrogen and that risk may persist after systemic HRT is stopped but this can still be explained by a growth-promoting effect. No arbitrary limits should be placed on the dose or duration of usage of HRT as decisions should be made on an individualised basis after discussing the benefits and risks with each patient. In addition to the potential increased risks of breast cancer and VTED, they should also be considered in the context of the overall benefits obtained from using HRT including symptom management and improved quality of life as well as the cardiovascular and bone protective effects associated with HRT. From a research perspective, there is need for large, long-term prospective randomised controlled trials using conventionally regulated bio-identical HRT and further research and development of new regimens.

Key points

1. In women with a low underlying risk of breast cancer (i.e. most of the population), the benefits of HRT for up to 5 years' use for symptom relief will exceed potential harm
 - Unopposed oestrogen is associated with no, or little change in risk but this may be influenced by age at initiation
 - There is no evidence of a dosage effect with oestrogen
 - Vaginal oestrogen is not associated with an increased risk
 - Combined HRT can be associated with an increased risk, which appears duration dependent
 - Whilst risk with continuous combined HRT may be greater than with sequential HRT, the difference in risk is small and may be offset by protection against endometrial cancer
 - Avoidance of synthetic progestogens in combined preparations may minimise risk
 - Risk is limited to lean women
 - Risk associated with HRT (including past users) is less than other lifestyle risk factors for breast cancer
 - In women with POI, years of HRT exposure should be counted from the age of 50
 - Communicating risk in terms of absolute excess risk with framing, minimizes misinterpretation

2. In women at high risk, or breast cancer survivors
 - There is no additive effect of HRT exposure in women at elevated personal risk due to a family history or high-risk benign breast condition.^{3,9}
 - If the use of HRT or vaginal oestrogen is considered, this should only be for the management of oestrogen deficiency symptoms after discussion with the woman's breast specialist team
 - Vaginal oestrogen can be used in women taking tamoxifen but not aromatase inhibitors.

References

1. Morris E, Currie H. Informed choice: Is it achievable? *Menopause Int*, 2011; 17: 115
2. Makama M, Drukker CA, Rutgers EJT et al. An association study of established breast cancer reproductive and lifestyle risk factors with tumour subtype defined by the prognostic 70-gene expression signature (MammaPrint®). *Eur J Cancer*. 2017; 75: 5-13
3. Collaborative Group on Hormonal Factors for Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence, doi.org/10.1016/S0140-6736(19)31709-X
4. Collaborative Group on Hormonal Factors for Breast Cancer. Breast cancer and hormone replacement therapy: Collaborative reanalysis from 51 individual epidemiological studies. *Lancet* 1997; 350: 1047–1060
5. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002; 288: 321–333
6. Anderson GL, Limacher M, Assaf AR et al; Womens's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. *JAMA*, 2004; 291: 1701-12
7. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; 362: 419–427
8. National Institute for Health and Care Excellence; Menopause; Clinical Guideline – methods, evidence and recommendations (NG23), 2015 www.nice.org.uk/guidance/ng23
9. Santen RJ and Yue W. Cause or prevention of breast cancer with estrogens: analysis from tumour biological data, growth kinetic model and Women's Health Initiative Study. *Climacteric* 2019, 22; 3-12
10. Shapiro S, Farmer RD, Stevenson JC et al. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies. Part 4: The Million Women Study. *J Fam Plann Reprod Health Care*, 2012; 38: 102-109
11. Gigerenzer G. How innumeracy can be exploited, In *Reckoning with Risk*, publishers Penguin Group, 2003
12. Wang K, Li F, Chen L, Lai YM et al. Change in risk of breast cancer after receiving hormone replacement therapy by considering effect-modifiers: a systematic review and dose-response meta-analysis of prospective studies. *Oncotarget*, 2017; 8: 81109-81124
13. The 2017 hormone therapy position statement of the North American Menopause Society. *Menopause: The Journal of The North American Menopause Society*, 2017; 24: 728-753
14. Marsden J. NICE guideline – Menopause: diagnosis and management. Long-term benefits and risks of HRT (Section 11): Breast cancer. *J Post Reprod Health*, 2016; 22: 85-91
15. Jareid M, Thalabard JC, Aarflot M et al. Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer, without increased risk of breast cancer. Results from the NOWAC Study. *Gynecol Oncol*, 2018; 149: 127-132
16. Soini T, Hurskainen R, Grénman S et al. Levonorgestrel-releasing intrauterine system and the risk of breast cancer: A nationwide cohort study. *Acta Oncol*, 2016; 55: 199-192
17. Yang Z, Hu Y, Zhang J et al. Estradiol therapy and breast cancer risk in perimenopausal and postmenopausal women: a systematic review and meta-analysis. *Gynecol Endocrinol*, 2017; 33: 87-92
18. The British Menopause Society consensus statement on the management of women with premature ovarian insufficiency, 2017. www.thebms.org.uk

19. Jaakkola S, Lyytinen H, Pukkala E and Ylikorkala O. Endometrial cancer in postmenopausal women using estradiol-progestin therapy. *Obstet Gynecol*, 2009; 114: 1197-1204.
20. Crandall CJ, Hovey KM, Andrews CA et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. *Menopause*, 2018; 25: 11-20
21. Cheblowski RT, Thomas RE, Manson JE et al. Breast cancer after use of estrogen plus progestin and estrogen alone. *JAMA*, 2015; 3: 296-305
22. Brown KF, Rungay H, Dunlop C et al. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer*, 2015; 118: 1130-1140
23. Manson JE, Chlebowski RT, Stefanick ML et al. The Women's Health Initiative hormone therapy trials: update and overview of health outcomes during intervention and post-stopping phases. *JAMA*, 2013; 310: 1353-1368
24. Suzuki R, Orsini N, Saji S et al. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status--a meta-analysis. *Int J Cancer*, 2009; 124: 698-672
25. Hamajima N, Hirose K, Tajima K et al. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer*, 2002; 87: 1234-1245
26. www.ons.gov.uk/deathsummarytables2017final-2 (accessed 9th December 2019)
27. Beral V, Peto R, Pirie K, Reeves G. Menopausal hormone therapy and 20-year breast cancer mortality, *Lancet*, 2019; [http://dx.doi.org/10.1016/S0140-6736\(19\)32033-1](http://dx.doi.org/10.1016/S0140-6736(19)32033-1)
28. Yu X, Zhou S, Wang J, Zhang Q et al. Hormone replacement therapy and breast cancer survival: a systematic review and meta-analysis of observational studies. *Breast Cancer*. 2017; 24: 643-657
29. Manson JE, Aragaki AK, Rossouw JE et al; WHI Investigators. Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. *JAMA*. 2017; 318: 927-938
30. Colleoni M, Sun Z, Price KN et al. Annual hazard rates of recurrence for breast cancer during 24 years of follow-up: results from the International Breast Cancer Study Group Trials I to V. *J Clin Oncol*, 2016; 34: 927-935
31. Holm M, Olsen A, Au Yeung SL et al. Pattern of mortality after menopausal hormone therapy: long-term follow up in a population-based cohort. *BJOG*, 2019; 126: 55-63
32. Sarrel PM, Njike VJ, Vinante V, Katz DL. The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. *Am J Public Health*, 2013; 103: 1583-1588
33. National Institute for Health and Care Excellence; Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer (CG164), 2013 www.nice.org.uk/guidance/cg164
34. Gordhandas S, Norquist BM, Pennington KP et al. Hormone replacement therapy after risk reducing salpingo-oophorectomy in patients with BRCA1 or BRCA2 mutations; a systematic review of risks and benefits. *Gynecol Oncol* 2019; 153: 192-200
35. National Institute for Health and Care Excellence; Early and locally advanced breast cancer: Diagnosis and treatment. NICE guidelines [NG101]. 2018 www.nice.org.uk/guidance/ng101/resources.
36. Swain SM, Wilson JW, Mamounas EP, Bryant J, Wickerham DL, Fisher B, Paik S, Wolmark N. Estrogen Receptor Status of Primary Breast Cancer Is Predictive of Estrogen Receptor Status of Contralateral Breast Cancer, *JNCI*, 96; 7: 516-523
37. Karlsson E, Lindström LS, Wilking U, Skoog L, Johansson U, Bergh J. Discordance in hormone receptor status in breast cancer during tumor progression. *J Clin Oncol* 2010; 28: no 15_suppl (May 20) 1009-1009. DOI: 10.1200/jco.2010.28.15_suppl.1009

38. Marsden J, Morden J, A'Hern R et al on behalf of the UK HRT Trial Management Group. Hormone replacement therapy (HRT) is effective in relieving oestrogen deficiency symptoms (ODS) and improves quality of life in breast cancer patients: The UK randomised HRT trial experience. *Maturitas* 2017; 132 DOI: <https://doi.org/10.1016/j.maturitas.2017.03.286> [Accessed 15th July 2018]
39. Kenemans P, Bundred NJ, Foidart JM et al. LIBERATE Study Group. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. *Lancet Oncol* 2009; 10: 135-146.